

## Clozapine products – Safety update

- On January 28, 2020, the [FDA announced](#) that they are strengthening existing warnings in the drug label for all clozapine products regarding clozapine-induced constipation that may progress to serious bowel complications.
- Serious bowel complications can lead to hospitalization or even death if constipation is not diagnosed and treated quickly. Constipation is a frequent and known side effect of clozapine, but serious and fatal events continue to be reported.
- Clozapine is sold under the brand names [Clozaril®](#), [Fazaclo® ODT](#), and [Versacloz®](#), and as generics by many different drug companies.
- Clozapine is indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment and for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state.
- Patients taking clozapine may not feel or be aware of constipation symptoms. A healthcare provider should be contacted if bowel movements are less frequent, the patient experiences hard/dry stools and difficulty passing gas, and if more serious symptoms occur such as nausea/vomiting, bloating or stomach pain.
- Constipation can be prevented by improvements in diet and lifestyle. The patient's healthcare provider may recommend a laxative as well. Patients should not stop clozapine therapy without first discussing with a healthcare provider.
- Healthcare providers should evaluate bowel function before initiating clozapine and avoid co-prescribing with other anticholinergic medicines that can cause gastrointestinal hypomotility. A prophylactic laxative may be considered in patients with a history of constipation or bowel obstruction.
  - The risk is greater with clozapine than the other schizophrenia medicines because of clozapine's potent anticholinergic activity.
  - The risk is further increased at higher doses of clozapine or when it is co-prescribed with anticholinergic agents and other medicines that cause constipation, including opioids.
- Patients should be counseled regarding the risk of constipation and life-threatening bowel issues and the need to stay hydrated to prevent constipation.
- The safety update is based on 10 cases from the FDA Adverse Event Reporting System database and the medical literature. These cases resulted in hospitalization, surgery, and five deaths. Adverse events included necrotizing colitis, intestinal ischemia or necrosis, and volvulus.
  - The total daily dose of clozapine administered ranged from 200 mg to 600 mg, with a median daily dose of 400 mg.

- The time to onset of serious bowel events ranged from 3 days to 6 months, with a median of 46 days.



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